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(54) Automated capillary electrophoresis apparatus.

(57) An automated apparatus and system for effecting capillary electrophoresis is disclosed. The system includes two conveyors for conveying septum sealed vials into registry underneath a cartridge containing a capillary for capillary electrophoresis. The capillary interior of the cartridge is wound in a serpentine path. The capillary depends at its two distal ends downwardly from the cartridge at two spaced apart locations from the bottom surface of the cartridge. The vials, each held in a vial holder, are conveyed until one vial on one conveyor underlies one depending distal capillary end and the other vial on the other conveyor underlies the other depending distal capillary end. Once registry of the vials to the distal capillary ends has occurred, the vials are moved upwardly – typically by piston assisted movement of vial holders with respect to the conveyors. Such upward piston assisted movement continues until the vials are pierced at a sealing septum by hypodermics. After piercing of the hypodermics, the piston assisted upward movement continues to thread the hypodermic with either a capillary or an electrode for access to the content to the interior of th vial. Th apparatus and process actuates a sequenc of vials to produce automated capillary electrophoresis. The sequenc includes charging th capillary at a first vial with electrolyte and thereafter injecting from a second and different vial a predetermined amount of sample into the electrolyte filled capillary. After sample injection the sequence includes causing paired third and fourth vials of electrolyte to be communicated to the depending ends of the capillary, communicating electrodes to each of the third and fourth vials to produce the required electric force for capillary electrophoresis and permitting the capillaries to be exposed at its distal ends to the electric forces for a sufficient period of time to cause sample classification due to the electrophoresis. Provision is made in the cartridge immediately adjacent one of the ends thereof for detection of the electrophoretically classified components. The detection schemes including fluorescence, light absorption or reflection, light deflection responsive to electrical changing optical index. Upon completion of the electrophoresis, the capillary is recharged with electrolyte and the process endlessly repeated using differing sequences of vial. The continued electrophoresis either uses the same capillary in the same cartridge or a differing capillary mounted to a different cartridge.

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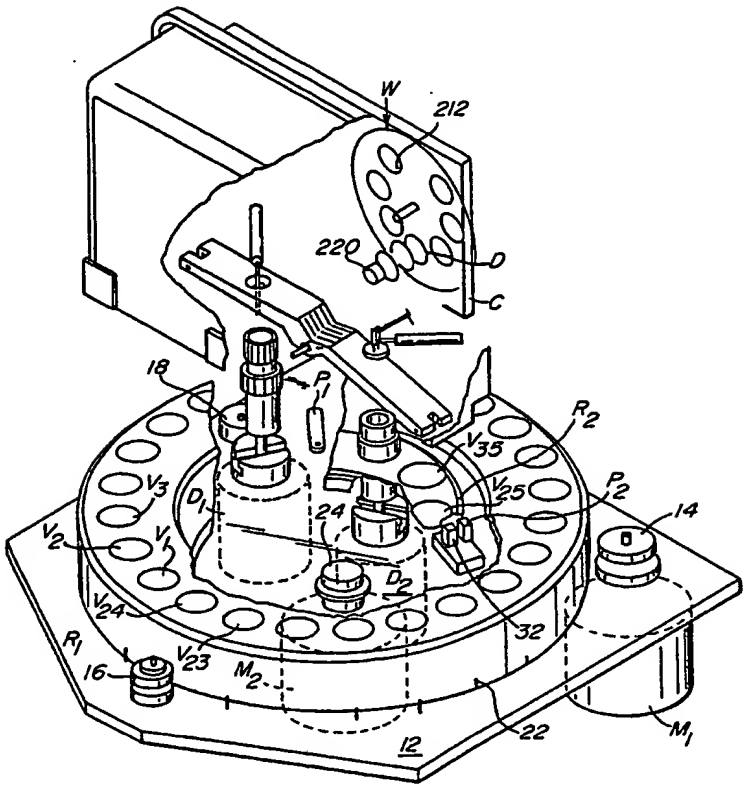
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D1
V25
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V2
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D2
V24
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R1
16
V23
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22
M1

FIG. 1A

AUTOMATED CAPILLARY ELECTROPHORESIS APPARATUS

This invention relates to capillary electrophoresis. More particularly, an apparatus is disclosed which automates capillary electrophoresis.

BACKGROUND OF THE INVENTION

Capillary electrophoresis is known. An electrolyte filled capillary is injected with sample. The two distal ends of the sample are each emerged in separate electrolyte baths. Each electrolyte bath is communicated with differing electrode potential sufficient for electrophoresis to occur in the capillary.

Electrophoresis is easy to understand. Typically, differing components of a sample subjected to electrophoresis have differing size and differing electric charge. Dependent upon the size of the particles and their charge, a migration of constituents of a sample occurs along the length of a capillary when the capillary is subjected at its distal ends to differing electrical potentials. The discrete particle migration through the capillary is the sum of two effects.

First, and assuming that the capillary is filled with an electrolyte, an overall flow of electrolyte can and does occur due to the difference in electrical potential across the length of the capillary.

Second, and relative to any overall induced flow in the capillary, individual particles of sample will move relative to one another. This movement constitutes the sought after classification due to electrophoresis.

It will be understood that the electrolyte filling in the capillary can be a liquid subject to overall flow or a gel, which is not usually subject to overall flow.

Typically the sample is placed adjacent one end of a capillary. A detector is placed adjacent the opposite end of a capillary. In the migration of the discrete sample constituents relative to the fluid in the capillary, the discrete constituents each form themselves into discrete flowing "bands". These discrete flowing bands are the product of the electrophoresis that are observed to determine both quantity and quality of the sample.

Statement of the Problem

There is a need to automat electrophor sis. If the technique can be automated to the point where vials sealed with sample can be automatically subjected to electrophoresis on a basis that is substantially remote, the technique of classification by the electrophoresis can be given an expanded application in analytical techniques.

The reader will understand that insofar as the recognition of the problem constitutes invention, invention is herein claimed.

SUMMARY OF THE INVENTION

An automated apparatus and system for effecting capillary electrophoresis is disclosed. The system includes two conveyors for conveying septum sealed vials into registry underneath a cartridge containing a capillary for capillary electrophoresis. The capillary interior of the cartridge is wound in a serpentine path. The capillary depends at its two distal ends downwardly from the cartridge at two spaced apart locations from the bottom surface of the cartridge. The vials, each held in a vial holder, are conveyed until one vial on one conveyor underlies one depending distal capillary end and the other vial on the other conveyor underiles the other depending distal capillary end. Once registry of the vials to the distal capillary ends has occurred, the vials are moved upwardly -- typically by piston assisted movement of vial holders with respect to the conveyors. Such upward piston assisted movement continues until the vials are pierced at a sealing septum by hypodermics. After piercing of the hypodermics, the piston assisted upward movement continues to thread the hypodermic with either a capillary or an electrode for access to the content to the interior of the vial. The apparatus and process actuates a sequence of vials to produce automated capillary electrophoresis. The sequence includes charging the capillary at a first vial with electrolyte and thereafter injecting from a second and different vial a predetermined amount of sample into the electrolyte filled capillary. After sample injection the sequence includes causing paired third and fourth vials of electrolyte to be communicated to the depending ends of the capillary, communicating electrodes to each of the third and fourth vials to produce the required electric force for capillary electrophoresis and permitting the capillaries to be exposed at its distal ends to the electric forces for a sufficient period of time to cause sample classification due to the electrophoresis. Provision is made in the cartridge immediately adjacent one of th ends thereof for detection of the electrophoretically classified components. The d tection schemes including fluor scence, light absorption or reflection, light d flection responsive to electrical changing optical ind x.

Upon completion of the electrophoresis, the capillary is recharged with electrolyte and the process endlessly repeated using differing sequences of vial. The continued electrophoresis either uses the same capillary in the same cartridge or a differing capillary mounted to a different cartridge.

Other Objects, Features and Advantages

An object of this invention is to disclose an apparatus and process for automated electrophoresis. Accordingly, at least two conveyors are loaded with vials. These vials are preferably septum sealed and registered to a cartridge containing a capillary. One vial on one conveyor is registered underneath a distal end of a capillary depending from a cartridge. The other vial on the other conveyor is registered beneath the opposite distal end of the capillary depending from the cartridge. The vials are thereafter moved vertically to pierce the septum, immerse the capillaries, in the fluid within the vials, and communicate electrodes to the fluid within the vials to effect automated electrophoresis.

A further object of this invention is to automate the injection of electrolyte, and sample to a capillary. According to this aspect, a series of vials are conveyed under one capillary end. A first vial is used to fill the capillary with electrolyte. A second vial is used to inject a small, precisely measured amount of sample. Once these injections have occurred, automated electrophoresis occurs.

An advantage of the disclosed apparatus is that electrophoresis can, for the most part, be automated. By the expedient of placing a series of vials in a conveyor, and appropriately programming the conveyor, sequential analysis of many samples can occur on an automated basis with minimal technician supervision.

A further advantage of the disclosed process is the disposition of a capillary in a cartridge. By the simple expedient of changing the cartridge, the size and length of the capillary can likewise readily be changed.

A further object to this invention is to disclose a preferred arrangement of the conveyor. Typically, two concentric and circular conveyors are provided. A first outer circular conveyor having in the order of 24 vials, supplies sequentially electrolyte, for charging the capillary, sample for injecting the capillary and electrolyte for providing electric charge to a depending distal ends of the capillary to cause electrophoresis. A second inner and circular conveyor having in the order of 10 vials supplies electrolyt for the requir d communication f lectric charge for the electrophoresis. As a result, th conveyors, when suitably programmed, can sequentially register vials for a series of electrophoretic classifications, these classifications being essentially remote.

An advantage of this asp ct of the invention is that the technician services needed for electrophoresis can be reduced to placing vials in the correct order on a conveyor. The sequential events after placement of the vials on the conveyor are all automated.

Yet additional object to this invention is to utilize septum sealed vials for the electrophoresis. According to this aspect, all vials on the conveyors whether including electrolyte or sample are sealed at septums. These septum sealed vials are maneuvered and registered under a cartridge at a distal capillary end and then moved upwardly to effect contact with the capillary. Contact with the capillary is caused by impaling the vial at the septum on hypodermics to penetrate through the septum and form a conduit to the contents of the vials. Once penetration of the septums by the hypodermics has occurred, the hypodermics are threaded with capillaries or electrodes. The threading of the hypodermic with the capillary permits charging of the capillary with electrolyte, the injection of sample and the communication of the end of the capillary to the contents of the vial. The threading of the remaining hypodermic with an electrode permits the communication of electric charge to the contents interior of the vial.

An advantage of this aspect of the invention is that the fluid in the vials are sealed until the moment of their use in the electrophoretic process. Consequently, the process and apparatus here shown is uniquely compatible with laboratory diagnostic routines. Septums sealed samples can await analysis at the disclosed apparatus and be processed at the conveyance of laboratory personnel.

A further object to this invention is to illustrate in combination with the cartridge contained capillary, optical detector apparatus. According to this aspect of the invention, a light source with a conventional condenser light train is focused to a detector bath on the analytical apparatus. The disclosed cartridge has two cylindrical protrusions; a first protrusion is for leveling the cartridge, and a second protrusion, placed adjacent the detector aperture in the cartridge, is for registering the detector aperture precisely to the detector light train. By the expedient of providing a filter wheel in the optics, rotating the wheel for the optimum detection, examination of the classified bands in a specimen subject to electrophoretic classification can result.

An important advantage of this asp ct of the invention is that most of the detector apparatus is combin d to the complex instrumentation exterior of the cartridg . Consequently, the cartridge con-

taining capillary is vastly simplified.

BRIEF DESCRIPTION OF THE DRAWINGS

Other objects, features, and advantages of this invention will become more apparent after referring to the following specification and attached drawings in which:

Figs. 1A and 1B are side-by-side perspective views of the apparatus of this invention illustrating the two concentric rotating tables containing septum sealed vials underlying a capillary contained cartridge with the cartridge being communicated to a source of forced circulation coolant for capillary cooling and a light train for optical capillary detection illustrated;

Fig. 2 is a view of the septum piercing hypodermic apparatus, this view being sufficient to understand the mechanics of vial access; and

Fig. 3 is a side elevation illustrating the bottom of an overlying cartridge with two septum sealed vials each in their own conveyor being registered for access to their sealed contents;

Fig. 4A4C are a cartoon-series illustrating in Fig. 4A cartridge contained capillary filled with electrolyte, in Fig. 4B the same cartridge contained capillary charged with sample and in Fig. 4C the capillary undergoing electrophoresis.

Referring to Fig. 1A a plate 12 has a first conveyor R1 rotatably mounted thereon between wheels 14, 16 and 18. Wheel 14 is rotatable with motor M1 and consequently causes the circular conveyor R1 to rotate as motor M1 turns wheel 14. A detector P1 observes notches 22 configured in conveyor R1. Precise positioning of the conveyor can be made.

Twenty-four vial holders V1-V24 are configured in the top of the conveyor R1. As will hereinafter be set forth, these vial holders are registered under a cartridge C at a depending capillary entrance. By having a plunger D1 cycle the vial holders upwardly and downwardly, sequential filling of the capillary with electrolyte, injection of measured amounts of sample, followed by electrophoresis can sequentially occur.

The operation of inner conveyor R2 is similar. Specifically a motor M2 drives a wheel 24 which along with other idler wheels (obscured from view) cause conveyor R2 to rotate. A position sensor P2 registers to grooves 32 in conveyor R2.

Conv yor R2 has vial apertures V1 through V10 configured in the top thereof. By registering the vials V1 through V10 adjacent the detector aperture of a cartridg C, th automated electrophoresis herein can occur. Once registry has occurred, a plung r D2 manipulates the vial upwardly for the automated el ctrophoresis disclosure set forth herein.

Referring to Fig. 2, it will be understood that conveyor R1 has caused an individual vial, in this case vial V6, to be conveyed in its respective holder H underlying a capillary Q. In this underlying position, plunger D1 grasping the bottom of the holder has moved holder H upwardly. Holder H and the vial V6 contained therein have been impaled upon two hypodermics. These hypodermics are hypodermic 40 containing an electrode E and hypodermic 42 threaded by the capillary Q.

The reader will understand that the same apparatus is repeated. Specifically, it repeats with respect to conveyor R2 and plunger D2.

Referring to Fig. 3, the disclosed apparatus can be seen in section. Referring to Fig. 3, two holders H are illustrated with respect to conveyors R1 and R2. Conveyor R1 has caused vial V6 to be positioned underneath hypodermic apparatus (it being noted that the second hypodermic 42 is hidden from view). Similarly, conveyor R2 has positioned vial V24 underlying hypodermic 60, (it being noted that a second electrode is hidden from view).

Referring back to the view of Fig. 1A, it can be understood that each vial and hypodermic apparatus underlies an exit of a cartridge. Specifically, two depending capillary ends 70 and 72 depend downwardly.

Referring back to Fig. 2, it can be understood that as the septum S of each vial is pierced, the respective capillaries pierce the septum. Once piercing of the septum has occurred, the respective hypodermics are threaded. At each vial, threading of one hypodermic occurs with capillary Q. At the other hypodermic, threading with an electrode E occurs.

Referring back to Fig. 3, it will be seen that hypodermic 40 communicates to a source of pressure in conduit 80. Likewise, hypodermic 60 communicates to a source of pressure 90. It will be understood that once registry of the holder H and piercing of the septum by the hypodermics 40, 42 occurs pressure communicated interior of vial V6 will cause flow in the capillary Q. This flow in the capillary Q will permit charging of capillary Q with electrolyte and thereafter charging of capillary Q with a measured amount of sample.

In order that this may be understood, the schematics of Figs. 4A, 4B and 4C will now be referred to.

Referring to Fig. 4A, a capillary Q contained in a cartridge C is illustrated. One distal end of capillary Q at 70 is disposed within vial V6. Th opposite distal end of the capillary Q is disposed within vial V24.

A conduit 100 suppli s pressur to the int rior

of vial 70. Since capillary nd 70 is below the level of electrolyt 90 contained within vial V6, the capillary Q fills with electrolyte. Filling occurs from end 70 to and towards end 72.

Referring to Fig. 4B, vial V6 has been replaced. It has been replaced by the conveyor mechanism with a new vial V7. Vial V7 contains sample.

Again pressure is applied to vial 70. The applied pressure forces the sample 92 into the beginning of the capillary.

Once sufficient sample 92 is injected at end 70 of capillary Q, replacement of the vials again occurs. A vial V8 filled with electrolyte is communicated with end 70 of capillary Q. Likewise, a vial V25 is communicated with end 72.

In the schematic of Fig. 4C, electrodes are shown. Specifically, an electrode E1 is shown communicating a positive charge to vial V8 filled with electrolyte 90. Likewise, an electrode E2 is shown communicating electric current to the contents of vial V22 filled with electrolyte 90.

In Fig. 4C, an attempt has been made to show the resultant classification. Specifically, portions of the sample at 101 and 102 have preceded from the original location of the sample adjacent end 70 of capillary Q to that portion of the capillary Q adjacent end 72.

A detector aperture D is shown adjacent end 72 of capillary Q. This detector aperture will here be illustrated as being interrogated by light. The reader will understand that alternate methods of interrogation including the measurement of electrical resistance and the removal of sample for mass spectroscopy may as well be used.

Attention will now be directed to the light train L and its examination of the results of the electrophoresis.

Referring to Fig. 1B, light train L can be observed. A light source 200 puts out a point source of light 201. Point source of light is incident upon a plane mirror 204 and a focusing spherical mirror 208. Focusing mirror 208 focuses the light at a wheel W.

Wheel W includes a series of filter colors 212. Colors 212 register to the cartridge C. At the detector aperture D light passes through the detector aperture D and onto photosensing equipment 220. It is at the photosensor that recordation of optical measurements can be made.

It will be appreciated that the disclosed instrument additionally includes the possibility of recording resistance as well as other measurements. Such other measurements, such as mass spectroscopy, can be accommodated by running the required electrophor sis in a cartridge C for a given period of time and thereafter removing the cartridge and extracting the concentrated sample bands.

This application has provided a summary of the combination of components illustrated resulting in th disclosed automated electrophoresis apparatus and process here shown. Separate portions of this apparatus and process have been covered in co-pending patent applications filed of even date herewith. Specifically, a patent application entitled Capillary Detector Cartridge for Electrophoresis filed 29 April 1988 as Serial No. 188,252 (Beckman Instruments Docket No. 8D-528) and assigned to the assignee herein completely sets forth possible constructions of the cartridge contained capillary.

Likewise, construction and operation of the vial holder is set forth in co-pending patent application filed of even date herewith. Specifically, a patent application entitled Vial Holder filed 29 April 1988 as Serial No 188,244 (Beckman Instruments Docket No. 8D-555) and assigned to the assignee herein sets forth construction of the vial holder and penetration of the septum of a vial held in the holder by the apparatus disclosed herein.

Finally, the apparatus and process for the injection of sample to a capillary filled with electrolyte is set forth in a co-pending patent application filed of even date herewith. Specifically, a patent application entitled Automated Capillary Injector filed 29 April 1988 as Serial No. 187,760 (Beckman Instruments Docket No. 8D-529) and assigned to the assignee herein sets forth a process and apparatus for the precision injection of precise amounts of sample to a capillary filled with electrolyte.

Claims

1. Apparatus for automated electrophoresis, said apparatus comprising:

a cartridge body having a bottom, said cartridge defining a serpentine path for receiving a capillary;

first and second spaced apart exits through the bottom of said cartridge, said exits communicated to the distal ends of said serpentine path;

a capillary wound to said serpentine path within said cartridge and having its two distal ends depending from the bottom of said cartridge at said spaced apart exits;

first and second vials for registration to said spaced apart distal ends of said depending capillary at said spaced apart exits;

said vials having a body for the containment of fluid with an upwardly disposed opening;

first and second conveyors for conveying vials, said first conveyor for conveying said first vial and having a first path under said first exit of said cartridge whereby a vial may b registered under a depending distal end of said capillary; said second conveyor for conveying said second vial having a

second path under said second exit of said cartridge whereby a second vial in said second conveyor can be registered under the other depending distal end of said capillary;
means for moving said first and second vial from registry under said exits of said cartridge to and from a position of penetration of said distal ends of said capillary at the opening of said vials whereby the depending distal ends of said capillary depending from said cartridge may be in fluid communication with the contents of said vial;
means for communicating electropotential to said vials whereby said cartridge when filled with electrolyte and sample undergoes electrophoresis between the distal ends of said two capillaries.

2. The invention of claim 1 and wherein said cartridge is detachably removable from said apparatus.

3. The invention of claim 1 and wherein said first conveyor contains a plurality of vials and said second conveyor contains a plurality of vials.

4. The invention of claim 1 and including detector apparatus registered to said cartridge:
said cartridge including an aperture for observing said capillary;
and means for passing light through said aperture for measurement of electrophoresis classified components within said capillary.

5. A process of electrophoresis comprising the steps of providing a capillary;
providing a cartridge body having a bottom;
mounting said capillary to said cartridge body so that the capillary protrudes from the bottom of said body at two spaced apart first and second exits;
providing a first conveyor for conveying a series of vials under said first exit;
providing at least three vials in said first conveyor, said first vial having electrolyte for filling said capillary, said second vial having sample for injection to said capillary and said third vial having electrolyte for providing electropotential for electrophoresis to one end of said capillary;
providing a fourth vial having electrolyte positioned under said second exit;
registering said first vial to said depending capillary at said first exit to immerse said depending end in electrolyte to fill said capillary with electrolyte;
registering said second vial to said depending capillary at said first exit to immerse said depending capillary in sample to inject a quantity of sample to said capillary:
simultaneously registering said third and fourth vials to the distal ends of said capillary to immerse the depending ends of said capillary in electrolyte;
and applying an electropotential across the third and fourth vials whereby the distal nds of said capillary produce electrophor sis along the length of said capillary.

6. The process of claim 5 wherein said registering step of said first vial includes sealing said first vial with respect to the bottom of said cartridge and applying pressure to said first vial whereby electrolyte from said first vial fills said capillary.

7. The process of claim 5 and wherein said registering step of said second vial includes seal said second vial with respect to the bottom of said cartridge and applying pressure to said second vial whereby sample is injected from said second vial to said capillary.

8. Apparatus for automated electrophoresis, said apparatus comprising:
a cartridge body having a bottom, said cartridge defining a serpentine path for receiving a capillary:
first and second spaced apart exits through the bottom of said cartridge, said exits communicated to the distal ends of said serpentine path;
a capillary wound to said serpentine path within said cartridge and having its two distal ends depending from the bottom of said cartridge at said spaced apart exits:
first and second septum sealed vials for registration to said spaced apart distal ends of said depending capillary at said spaced apart exits;
said vials having a body for the containment of fluid with an upwardly disposed opening;
first and second conveyors for conveying vials, said first conveyor for conveying said first vial and having a first path under said first exit of said cartridge whereby a vial may be registered under a depending distal end of said capillary; said second conveyor for conveying said second vial having a second path under said second exit of said cartridge whereby a second vial in said second conveyor can be registered under the other depending distal end of said capillary;
means for moving said first and second vial from registry under said exits of said cartridge to and from a position of penetration of said distal ends of said capillary at the opening of said vials whereby the depending distal ends of said capillary depending from said cartridge may be in fluid communication with the contents of said vial;
means for piercing said septum sealed vial position between said capillary and said vials, said piercing mean including a hypodermic threaded by said capillary;
means for communicating electropotential to said vials whereby said cartridge when filled with electrolyte and sample undergoes electrophoresis between the distal ends of said two capillaries.
said communication means including an electrode threading said hypodermic.

9. Th invention of claim 8 and wherein said means for communicating electropotential includes a second hypodermic and an lectrode threading said second hypodermic.

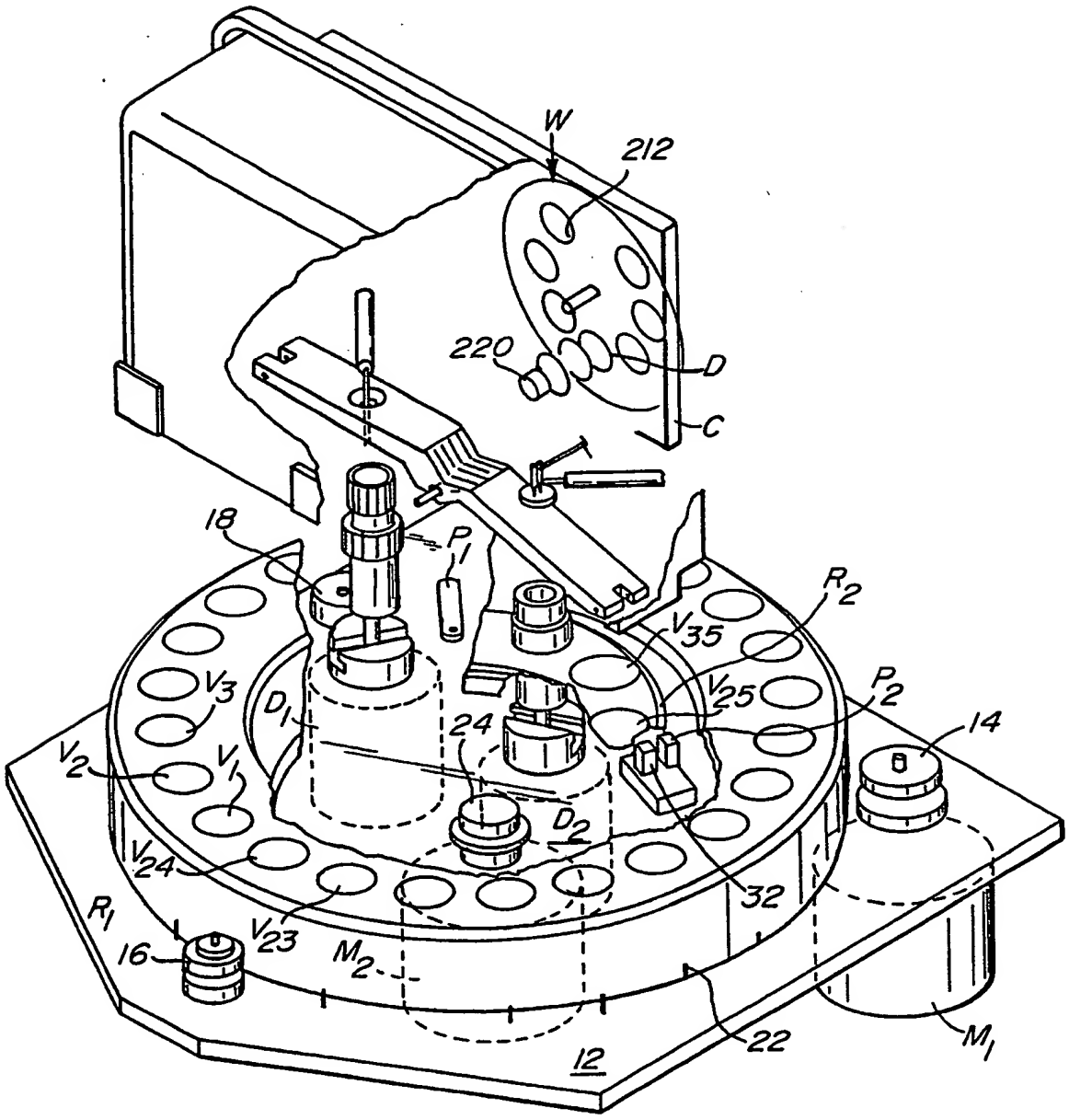
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FIG. 1A

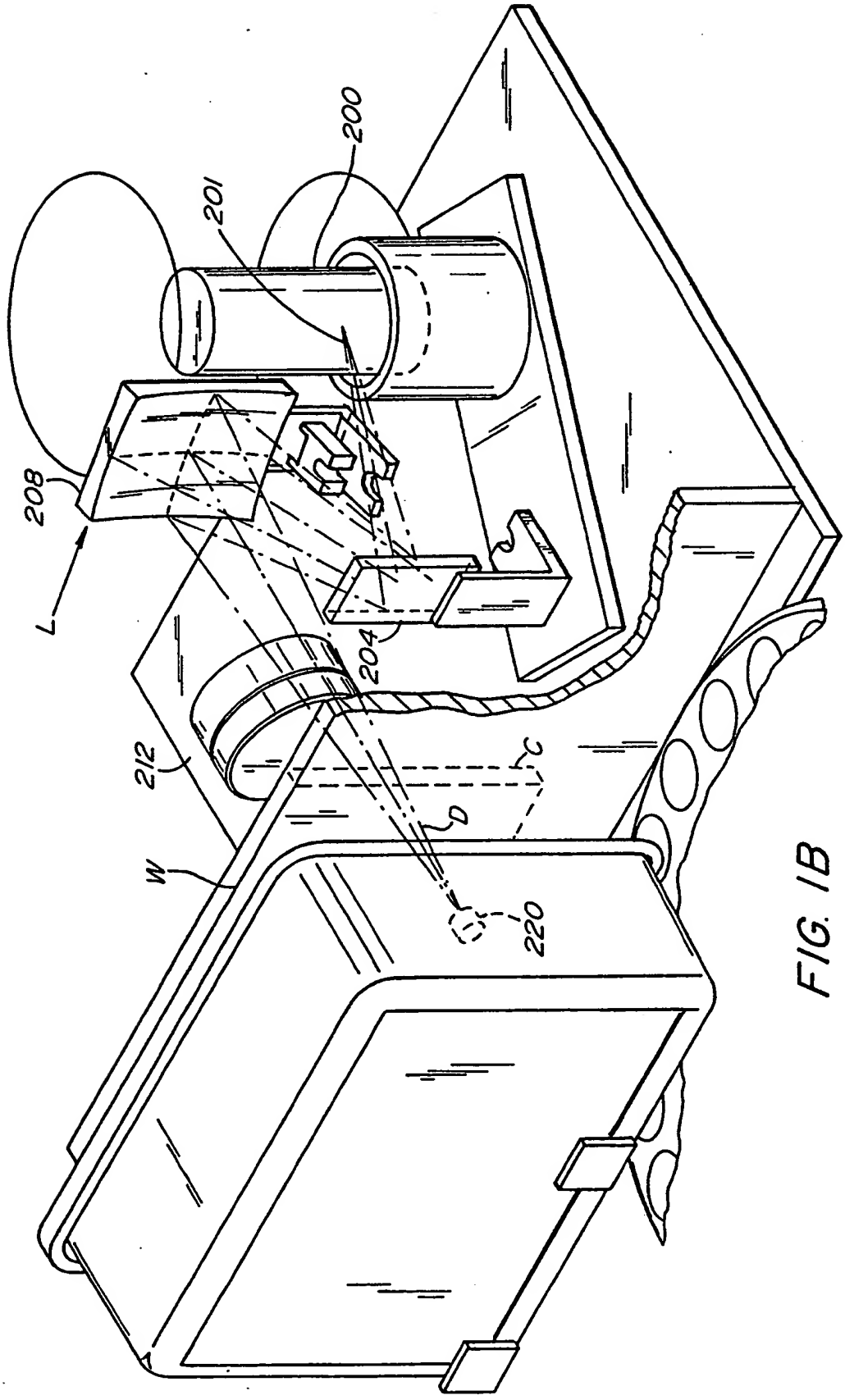

FIG. 1B

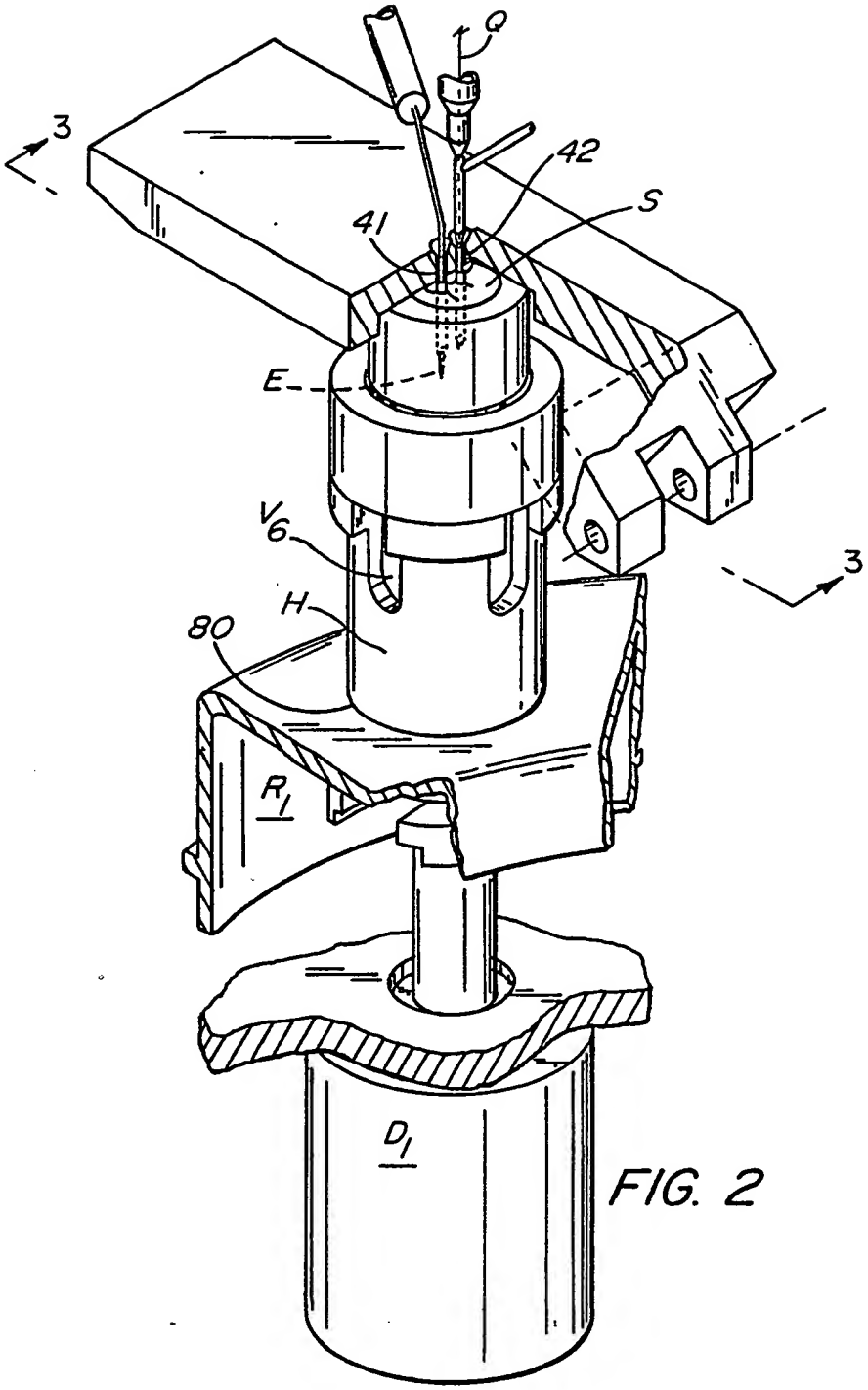

FIG. 2

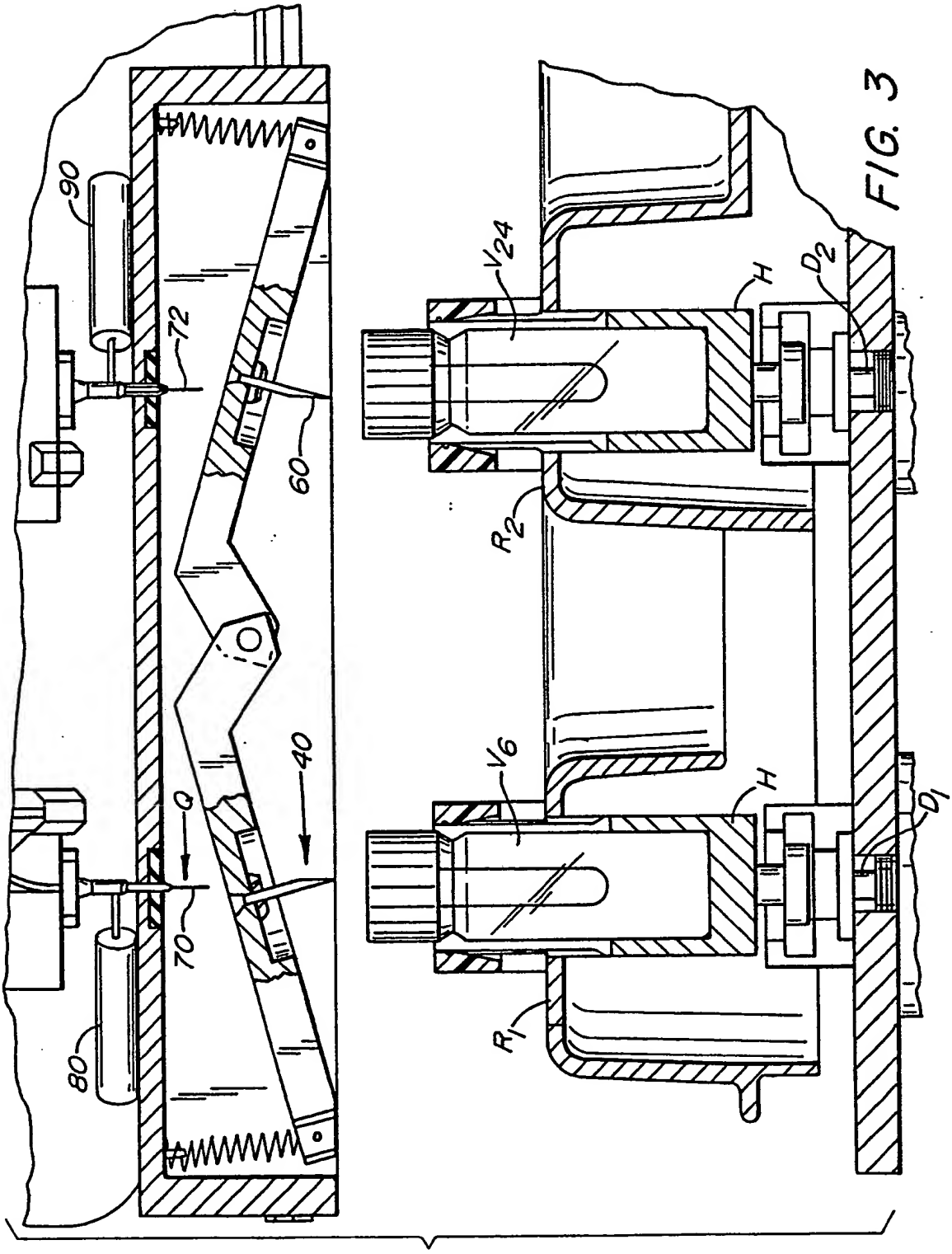

FIG. 3

FIG. 4A

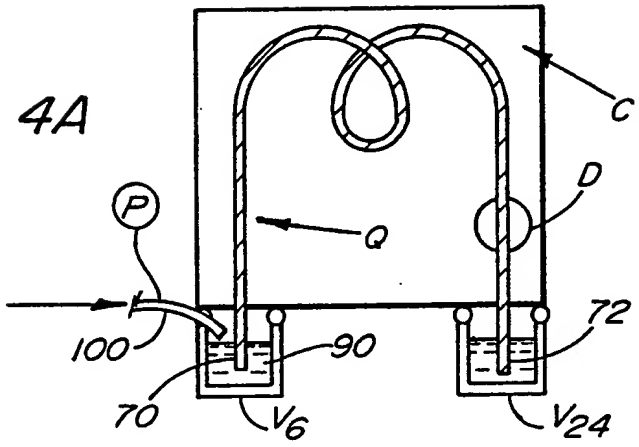

FIG. 4B

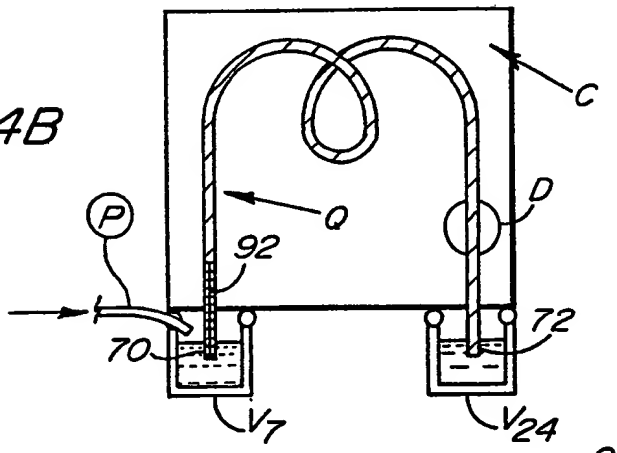

FIG. 4C